AdvaMed
Advanced Medical Technology Association

Clinical Laboratory Improvement Amendments of 1988 (CLIA) Criteria for Waiver; Industry Proposal

I. INTRODUCTION

This document is a proposal for criteria for device manufacturers submitting CLIA waiver requests to FDA. The criteria for waiver in this document, if accepted, would supersede those included in the Notice of Proposed Rulemaking (NPRM) published by the Health Care Financing Administration (HCFA/CMS) on September 13, 1995 (60 FR 47534).

BACKGROUND -- Since February 2000, FDA has had separate, but coordinated, responsibility for administering the provisions of both the Federal Food, Drug & Cosmetic Act (FDCA) and CLIA as each statute affects the commercialization by manufacturers and use by clinical laboratories of *In Vitro* Diagnostic (IVD) products. Under the FDCA, FDA imposes unique and rigorous requirements on companies that commercially distribute IVD instruments, kits and test systems, with particular attention to assuring that each manufacturer provides adequate instructions for labeled "intended uses" in the hands of intended users (21 CFR Sec. 809.10, access at http://frwebgate3.access.gpo.gov/cgi-bin/waisgate.cgi?WAISdocID=76562912739+1+0+0&WAISaction=retrieve). Under CLIA, FDA determines which regulated IVD products shall be categorized into the moderate and high complexity designations for purposes of assessing CLIA compliance by clinical laboratories. Further, FDA is responsible for determining which IVD products regulated by FDA qualify for waiver status under CLIA.

The CLIA statute, 42 U.S.C. Section 263a (d) (3) Examinations and Procedures, as modified by the Food and Drug Modernization Act of 1997 (FDAMA), reads:

> 'The examinations and procedures [eligible for certificates of waiver] are laboratory examinations and procedures that have been approved by the Food and Drug Administration for home use or that, as determined by the Secretary, are simple laboratory examinations and procedures that have an insignificant risk of an erroneous result, including those that - (A) employ methodologies that are so simple and accurate as to render the likelihood of erroneous results by the user negligible, or (B) the Secretary has determined pose no unreasonable risk of harm to the patient if performed incorrectly.'

The legislative history accompanying FDAMA clarifies that (A) and (B) above are examples of product types that could satisfy the criteria for waiver. However, since the Final Rule on IVD categorization was published in 1992, CMS, the Centers for Disease Control and Prevention (CDC), and FDA have agreed that a determination that a test may be waived can be based on criteria for "simple and accurate" other than those included in subparagraphs (A) and (B).

In addition, by matter of law, any IVD device cleared or approved by FDA for over-the-counter (OTC) or prescription home use automatically qualifies for waiver. This document provides a detailed description of the types of sound scientific evidence that support waiver requests. If the manufacturer chooses to use these criteria, then FDA will determine whether these criteria for waiver have been met.

This document outlines a systematic, step-wise approach for reviewing of products for CLIA waiver:

Step 1: Determine that the test is simple as defined in Section II of this document. (Whenever feasible, sample(s) of the test system should be included with the manufacturer's request for waiver.)

Step 2: Determine that the test has an insignificant risk of erroneous result by the end user as defined in Section III of this document. IF FDA determines that the test is simple (step 1) and there is an insignificant risk of an erroneous result by the end user (step 2), THEN it is a candidate for waiver. Error detection and alert mechanisms may help to assure that a test will have an insignificant risk of an erroneous result in the hands of end users.

Step 3: Determine that the test is accurate as defined in Section IV of this document. IF FDA determines that the test is simple (step 1), and there is an insignificant risk of an erroneous result by the end user (step 2), and it is accurate (step 3), THEN it meets the criteria for waiver.

Step 4: For all tests that meet the criteria for waiver, FDA will review the labeling (under 21 CFR Section 809.10) to ensure that it is consistent with these waiver requirements. Then FDA will issue a notification of waiver, also notifying CMS to ensure timely and proper CLIA survey and inspection reviews. Test systems approved for waiver will be published on FDA's website.

TERMS USED IN THIS DOCUMENT

Lay-user	a person with no professional laboratory education or on-the-job training or hands-on experience in conducting clinical laboratory tests. (Note: a user of an OTC test kit could be a lay-user.)
Laboratory professional	a person with professional laboratory education and/or on-the-job training and experience in conducting clinical laboratory tests. (Note**:** ***professional*** and ***laboratory professional*** are used interchangeably in this document)

II. DEMONSTRATING "SIMPLE"

A test is considered to be simple when the test has all of the following characteristics:

- Is a fully automated instrument, unitized, or self-contained test
- Requires only basic, non-technique-dependent specimen manipulation

- Requires only basic, non-technique-dependent reagent manipulation
- Has no operator intervention during the analysis
- Requires no technical or specialized training with respect to troubleshooting (interpreting error codes does not constitute troubleshooting)
- Requires no electronic or mechanical maintenance
- Provides a direct readout of results, i.e. requires no calculation or conversion.

Examples of these characteristics of simple tests include, but are not limited to, tests that:

- use capillary or whole blood, plasma, serum, urine, or swabs from a variety of locations
- require only simple reagent mixing steps, such as 'mix reagent A and reagent B'
- produce results that are read as `positive or negative'
- produce results that are read as a numerical value
- produce results determined by the clear presence or absence of a line
- produce results determined by obvious color gradations
- contain instructions for use written at no higher than a 7th grade reading level

Manufacturers may find it helpful to review these FDA documents about labeling and device design. They are available on the Internet as shown:

- "Write it Right," www.fda.gov/cdrh/dsma/897.pdf
- "Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management," www.fda.gov/cdrh/humfac/1497.html
- "Draft Document on Medical Device Patient Labeling," wwwfda.gov/cdrh/humfac/1128.html

III. DEMONSTRATING "INSIGNIFICANT RISK OF ERRONEOUS RESULT BY THE USER"

All laboratory tests have potential for error. Manufacturers routinely assess their tests and systems for potential errors through risk assessments, and implement various types of mechanisms to mitigate any identified risks. FDA routinely reviews the risk assessments as part of the 510(k) premarket notification review.

For waived tests, manufacturers need to assess whether moving the performance of the test from the professional user to the lay-user introduces any new risk of erroneous results. If any new risks are identified, manufacturers must implement mechanisms to mitigate the new risks. Examples of these mechanisms include, but are not limited to: error detection mechanisms, training programs, quality control checks, or modified instructions for use. It is the responsibility of each manufacturer to provide evidence that its risk mitigation mechanisms are effective. Risk mitigation and error detection methods cannot be 100% effective, however. Therefore, FDA must consider the unavoidable remaining risk versus the expected patient care benefit of having rapid access to a test, with appropriate labeling to guide physician decision-making in the waived testing environment.

IV. DEMONSTRATING "ACCURATE"

Most waived test systems are simple, rapid tests run at the so-called "point-of-care" (POC), that is with clinicians, laboratory professionals, or lay-users actually running the test and the supervising physician deciding on appropriate use of the test results while the patient is present and still being evaluated. Many of the currently waived test systems were specified by name by Congress in the 1988 statute in recognition of the need to maintain physician and patient access to such rapid POC tests to enhance patient care. CMS and FDA have expressed the concern that access to both established waived test systems and innovative new ones for immediate use by physicians not be impeded by CLIA waiver policies. Therefore, based on legislative history and Congress' clear intentions with FDAMA amendments to CLIA, industry proposes that CMS and FDA interpret "accurate" for purposes of CLIA waiver categorization to mean the following:

> (1) data from lay-user studies show that the performance of the test system is comparable and traceable to test results obtained with a higher-order laboratory method (as described in prEN ISO 17511), and
>
> (2) a lay-user, working only with a manufacturer's instructions for use (under 21 CFR Section 809.10), can reasonably be expected to obtain substantially equivalent test results as a professional laboratorian using the same instructions for use.

One or more lay-user studies are needed to demonstrate that the candidate product meets both of the waiver accuracy criteria. Manufacturers should include the following points when designing and conducting their lay-user study:

Universal Precautions
The manufacturer should conduct CLIA waiver studies under conditions that comply with Occupational Health and Safety Administration (OSHA) regulations pertaining to biological hazards ("universal precautions"), 29 CFR 1910.1030.

Financial Disclosure
If clinical investigators are involved in the study, a Financial Disclosure Statement may be required. For advice on whether the financial disclosure rule applies, please refer to CDRH's "Document for Industry: Financial Disclosure by Clinical Investigators", ww.fda.ogv/oc/document/financialdis.html, or the final rule on Financial Disclosure published in the Federal Register, February 2, 1998 (63 FR 5233).

Instructions for Use
The manufacturer should provide the lay-users with only the instructions for use normally provided with the product, e.g., Operators' Manuals, package inserts, or videos. Lay-users should receive no training, coaching, prompting, or written or verbal instructions beyond the normally provided instructions. They should have no opportunity to discuss the test with or otherwise coach or observe each other.

Demographic Data

The manufacturer should enroll individuals who represent anticipated users. Record each participant's occupation, to ensure that participants meet the definition of lay-users. While the participants' occupations should be diverse, they need not be representative of the general population. Collect and tabulate the demographic data shown below in the request for CLIA waiver.

- age
- gender
- education (including experience and training)

Number of Subjects

Manufacturers should determine the appropriate number of subjects on a case-by-case basis through a statistical approach. It is the responsibility of each manufacturer to design the proper study to assure that the number of samples reaches statistical significance.

Lay-user Comparison Study

Conduct the lay-user comparison study on a statistically significant number of suitable specimens. For quantitative tests, these specimens should be equally distributed across the reportable range of the test. For qualitative tests, specimens should be included for negative, positive, and near-cutoff values. At least 10% of the specimens should be near the cut-off. When available, actual patient specimens provide suitable material. However, where impractical, hazardous, or distributed insufficiently to challenge the reportable range, the manufacturer may substitute or supplement actual patient specimens with spiked or otherwise prepared materials consistent with the intended use of the device. Describe how the materials were prepared and how the assigned values were determined.

Each lay-user should test one masked specimen or prepared material. Keeping the value and lay-user's result masked, each specimen or prepared material should then be analyzed by a laboratory professional using a higher-order laboratory test.

Data Analysis for Quantitative Tests

Compare the results from the lay-users with the results from the higher-order laboratory method by a statistically appropriate method, e.g., Deming regression. The following information should be provided:

- Scatter plot of the results (untrained user on the y-axis, laboratory results on the x-axis) with the 45 degree line (y=x) and the regression line superimposed,
- Descriptive statistics, including the number of data pairs, mean, standard deviation, minimum, median, and maximum, and
- Regression estimates of slope and intercept (based on a ratio of variances equal to one), and the respective 95% confidence intervals.

A description of the study and the results of the study should be reported in the product labeling.

Data Analysis for Qualitative Tests

The study should demonstrate that lay-users obtain results that are comparable to the higher-order laboratory method, as defined by the manufacturer's acceptance criteria. Construct a 2 x 2 table as shown below to report the test results. Calculate the percentage of concordant and discordant results as shown below, and report these results, along with the 2x2 table, in the product labeling.

Table 1

Lab Results or Expected Results

	Positive	Negative
Waived test Positive	A	B
Waived Test Negative	C	D

Concordant (%) = (A+D)/(A+B+C+D) * 100

Discordant (%) = (B+C)/(A+B+C+D) * 100

Study Reports and Product Labeling

Provide a report of each study that is performed. Reports should include the protocol, numbers of subjects studied, procedures for subject selection and exclusion, description of the subject population, description of how specimens were collected and stored, discontinuations, complaints, device failures and replacements, pertinent tabulations, and clear descriptions and presentations of the statistical analyses. When applicable, results should be reported by site as well as overall. "Outliers" should not be removed. In the event that a part of the collected data is not included in the analyses, that fact should be clearly identified and justification should be given. The manufacturer should provide an annotated line listing of the data, and should be prepared to provide electronic versions of data sets.

Manufacturers should be prepared to justify the selected acceptance criteria, based upon statements of clinical need reported in peer-reviewed literature, published by medical specialty groups, or supported by recognized experts in the clinical field.

In reporting the statistical analysis of the accuracy studies in the product labeling, the manufacturer should ensure that the section is written in a way that is clear and understandable to the health care professional who will be interpreting and acting upon the test result. Clinicians need to be able to assess, by reading the product labeling, whether the test is suitable for use in their practice. Consult FDA's "Write it Right" (www.fda.gov/cdrh/dsma/897.pdf) for assistance.

Policy Objectives

This flexibility in implementing "accuracy" criteria for waived test systems ties directly to the underlying CMS policy of being both "sensible" and "outcomes-oriented" in CLIA implementation (expressed in the preamble to its 1998 Final Rule on laboratory inspections):

> " . . .we are redirecting the HCFA inspection process to focus more on outcomes, rather than a solely process-oriented review. * * * [This] is a sensible means of allowing greater flexibility than the program currently provides. * * * Surveyors will review laboratory performance from the perspective of the effect on patient care rather than a line-by-line comparison for regulatory compliance." (63 FR 26722, May 14, 1998)

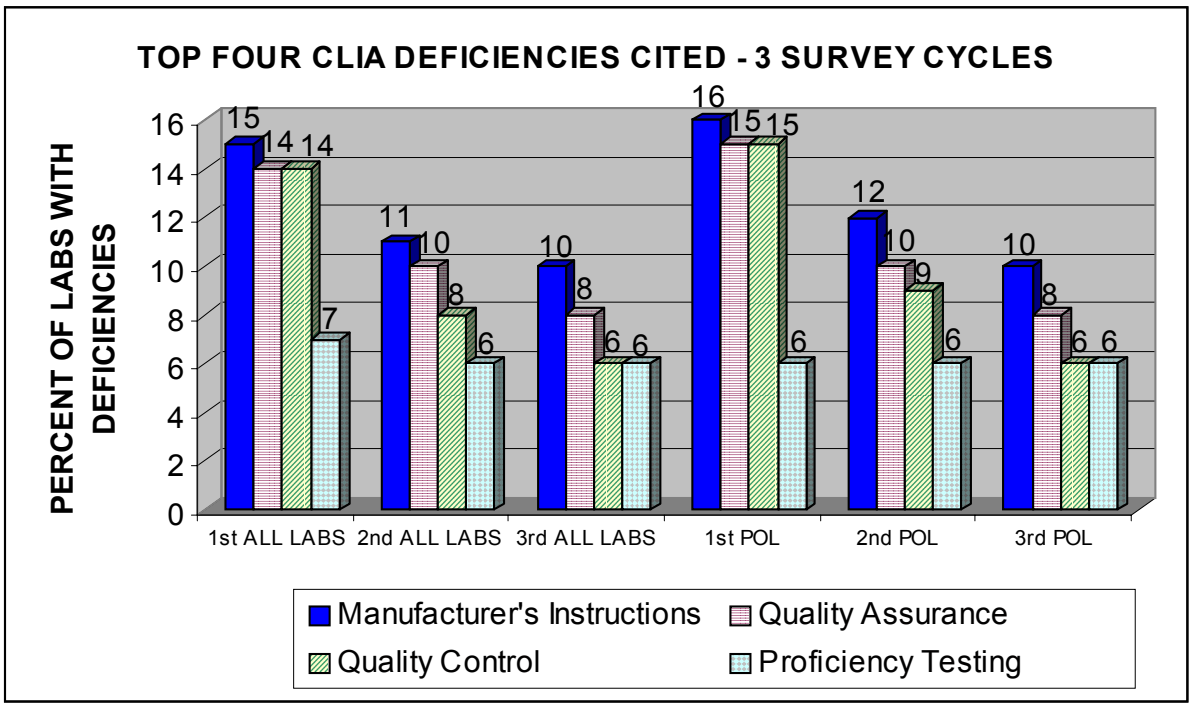
In sum, the policies advanced with this proposal include:

- Truth in labeling. FDA's core mission under both the FDCA and CLIA is to assure "truth in labeling" for regulated products. FDA fulfills its CLIA mission (under 42 CFR Section 1202) by assuring that clinicians and lay-users of waived test systems are provided easy-to-read and easy-to-follow ("simple") instructions for use of IVD products that perform well when compared to a higher-order test and are as reliable in lay-user hands as in professional hands ("accurate"). It is the manufacturer's responsibility to truthfully report the test system's accuracy, as compared to a higher-order method, and to report that accuracy in a way that can be understood by the physician using the waived test result. It is then the physician's responsibility to determine whether an individual test system, whether waived or not, performs adequately for use with his or her population of patients.

- Accessibility for innovators. By allowing innovators to prove accuracy as defined in this document, all analytes become eligible for waiver, so long as the other criteria set out here are met.

V. DEMONSTRATING END USER COMPETENCY

Recent data reported by CMS and the DHHS Office of the Inspector General show that physician office laboratories ("POL" in chart below) perform as well as "All Labs" in terms of compliance with CLIA requirements to have and follow each manufacturer's instructions for use of its waived test systems. That finding reinforces the determination of CMS and FDA to remind all laboratories and laboratory supervisors that it is imperative that they have and follow all manufacturers' instructions for use of test systems. Further, it is the laboratory director or supervising physician (in a POL setting) that is responsible for assuring that users of waived test systems--and all laboratory test systems--are competent.



Source: http://www.cms.gov/clia/stat4def.pdf

Reasonable quality control steps can be implemented for waived tests under CLIA that (1) allow end users to evaluate test kit integrity and (2) may evaluate end user competency. However, these two regulatory objectives must be addressed separately for purposes of CLIA regulation of waived test systems and certificate of waiver laboratories.

It is each manufacturer's responsibility to recommend quality control mechanisms, according to a risk analysis for an individual product, to reduce the risk of test system failure. The manufacturer is required to assure that the recommended QC measures employed to evaluate test kit integrity are clear to end-users. It is the laboratory director's (or supervising physician's) responsibility to establish competency assessment measures for test system users. Manufacturers cannot be expected to assure end user competency.

Under CLIA, the laboratory director is also responsible for (1) selecting test systems suitable for his or her practice, (2) making sure that the laboratory he or she supervises has and follows each waived test system manufacturer's instructions for use, and (3) consistently employing those Good Laboratory Practice (GLP) principles relevant to that individual laboratory's needs.